Selenium in diet, blood, and toenails in relation to human health in a seleniferous area[1,2]

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ABSTRACT To determine whether high dietary selenium intake was associated with adverse effects, selenium in diet, blood, and toenails was studied in relation to human health in adults residing in western South Dakota and eastern Wyoming. Over a 2-y period 142 subjects were recruited from households selected at random and from ranches where unusually high selenium intakes were suspected. Subjects completed health questionnaires, underwent physical examinations, provided blood samples for clinical assessment, and provided blood, urine, toenails, and duplicate-plate food collections for selenium analysis. About half of the 142 free-living subjects had selenium intakes > 2.54 μmol/d (200 μg/d) (range 0.86–9.20 μmol/d, or 68–724 μg/d). Physical findings characteristic of selenium toxicity were not present nor were clinically significant changes in laboratory tests or frequency of symptoms related to selenium in the blood, toenails, or diet. We found no evidence of toxicity from selenium in subjects whose intake was as high as 9.20 μmol/d (724 μg/d). *Am J Clin Nutr* 1991;53:1288–94.

KEY WORDS Selenium, toxicity, humans

Introduction

Selenium intake has been found to be related inversely to risk of heart disease and cancer in some epidemiologic studies (1, 2). As a consequence, interest in determining the maximum dose of selenium that may safely be ingested chronically has increased. Nonetheless, benefits of increasing selenium intake, if any, have not been established (1).

To determine whether the selenium consumed by persons residing in a seleniferous area might be associated with subtle indications of toxicity, we studied selenium dietary intake and concentration in blood and toenails in relation to health status in subjects residing in the South Dakota area. South Dakota is unusual because it has seleniferous topsoil in arable regions, leading to high concentrations of selenium in many of the foods produced there (3). In the 1930s selenosis in livestock was prevalent in several parts of the state (4) and may have occurred in humans (5, 6). In the current study, observations included a general health assessment, with special attention to abnormalities observed by others in overt cases of selenium toxicity, eg, loss of nails, neurologic abnormalities, and abnormal liver-function tests (7–9).

Subjects and methods

Subjects

The study was conducted over 2 y. In the first year (1985–1986) subjects came from two sources: households selected at random from telephone books for western South Dakota and eastern Wyoming' and ranches where unusually high selenium intakes were suspected because of current or previous selenosis in livestock. The ranches were identified through discussions with South Dakota residents, by use of geologic maps indicating seleniferous rock formations, and by use of maps showing areas where selenosis in livestock was reported in the 1930s (4).

In the second year (1986–1987) we identified an additional group of subjects suspected of having high selenium intakes (also because of previous or current selenosis in livestock) and measured their serum selenium concentrations. Subjects from ranches where at least one adult had a serum selenium concentration > 2.10 μmol/L were enrolled in the study. Average serum selenium concentrations in the United States are ~1.27–1.78 μmol/L (10, 11).

The study protocol was approved by the human subjects committees of the National Cancer Institute, the US Department of Agriculture, and the Harvard School of Public Health. Informed consent was obtained from all participants.

Data collection

Subjects were studied while they were living in their homes. In households with a spouse pair, both the husband and wife were enrolled. The schedule for data collection is shown in **Table 1**. The major differences in schedules between the first year (year 1) and the second year (year 2) of the study were that in year 2

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TABLE 1
Data-collection protocol

	Year 1 (1985–1986) (n = 78 subjects)				Year 2 (1986–1987)* (n = 64 subjects)			
	Summer	Fall	Winter	Spring	Summer	Fall	Winter	Spring
Blood (routine chemistry tests, blood counts, and liver-function tests)	+				+			
Symptom questionnaire	+	+	+	+	+		+	
Physical examination	+							
Nail photographs	+				+			
Blood and urine	+	+	+	+	+		+	
Toenails	+	+	+	+	+		+	
2-d duplicate portions of food and beverages saved†	+	+	+	+	+		+	
2-d diet records	+		+	+	+		+	
Diet questionnaire	+			+	+		+	

* The subjects studied in year 1 and year 2 were not the same.
† One subject per household.

the frequency of data collection was reduced to two seasons from four, and no general physical examinations were performed.

The standardized physical examinations were performed by a physician (MPL). Particular attention was paid to the dermatologic and neurologic examinations. For example, signs of interest included muscle weakness, asymmetrical reflexes, hyperreflexia, abnormal sensory examination, dermatitis, and nail loss or markings. A complete list of the items in the physical examination is given in the Appendix.

The self-administered questionnaire inquired about the frequency of symptoms that might reflect selenium toxicity. Symptoms of particular interest were weakness, paresthesias, dyspepsia, loss of hair or nails, and dermatitis (*see* Appendix for a complete list of symptoms). The questionnaire also included questions on demographic and anthropometric data, smoking, and food sources.

On nonconsecutive days, one subject (always the same) from each household saved duplicate portions of all foods and beverages consumed (Table 1). One-quarter of the food collections were on Saturdays or Sundays. Twenty-four–hour urine samples were collected on the day of the second food collection of the season. Blood specimens were drawn the day after the second food collection, after an overnight fast. When one member of the household saved duplicate food portions, both participating members of the household kept diet diaries. Subjects' toenails were collected at the time of each home visit.

Methods

The duplicate food portions were kept refrigerated or frozen until homogenized at Rapid City Regional Hospital in Rapid City, SD. Samples of the food homogenates were frozen at −9 °C and sent via overnight mail on dry ice to the Human Nutrition Research Center of the USDA in Beltsville, MD. Fasting venous blood samples were drawn into trace element–free evacuated tubes (VACUTAINER, Becton Dickinson, Lincoln Park, NJ). Samples of 24-h urine collections, whole blood, and serum were frozen in Rapid City and sent to Beltsville. Nail samples (clippings from all toes) from each subject were placed in envelopes and mailed to Boston where they were cleaned with ultrasound in a bath of distilled water, dried, and sent to the University of Missouri at Columbia.

All blood tests, except selenium analysis, were performed by using standard methods at the Black Hills Clinical Laboratory in Rapid City, SD. A hematologic examination (complete blood count), evaluation of prothrombin time, and serum chemistry tests, including aminotransferases and γ-glutamyl transferase (GGT), were completed. A complete list of the laboratory analytes examined is in the Appendix.

Selenium content of serum, whole blood, urine, and diet was determined by using an isotope-dilution technique and gas chromatographic–mass spectrometric analysis; sample preparation, digestion, and analysis was described elsewhere (12). The analytical blank for all samples averaged 3.81 pmol Se. The detection limit of the method (defined as the mean of the analytical blank plus three times the SD) was 6.36 pmol Se. Quality control was maintained by regular determinations of in-house reference pools of serum, whole blood, and urine. The coefficient of variation (CV) for duplicate analyses of the in-house reference pools was always < 2%.

The selenium content of toenail specimens was determined by neutron-activation analysis (13). The concentration of selenium in the National Institute of Standards and Technology (Gaithersburg, MD) Standard Reference Material 1577 (bovine liver), determined by neutron-activation analysis, was 14.1 ± 0.6 μmol/kg ($\bar{x} \pm$ SD) as compared with a certified value of 14 ± 1 μmol/kg. The CV for 38 repeated measurements was 4.5%.

Photographs of subjects' thumbnails were taken with a camera equipped with a macro lens and a ring light. A board-certified dermatologist, unaware of the subjects' laboratory results, evaluated the photographs. Abnormalities were recorded on a standardized form.

Statistics

The average concentration of selenium in whole blood, serum, urine, and toenails was calculated for each subject. For subjects studied in year 1, the average was calculated from four values; for subjects studied in year 2, the average was calculated from two values. Average dietary intakes of selenium were calculated

TABLE 2
Selenium concentration in whole blood, serum, toenails, 24-h urine, and diet for all subjects by year of study and recruitment strategy*

	All subjects (n = 142)	Year 1, selected at random (n = 49)	Year 1, ranchers (n = 29)	Year 2, screened ranchers (n = 64)
Whole blood (μmol/kg)	4.04 ± 1.39	2.95 ± 0.38	3.92 ± 1.09	4.96 ± 1.37†
	3.57 (2.30–8.54)	2.97 (2.30–4.36)	3.75 (2.71–7.22)	4.53 (2.68–8.54)
Serum (μmol/L)	2.50 ± 0.70	1.95 ± 0.20	2.44 ± 0.57	2.95 ± 0.69†
	2.33 (1.56–4.60)	1.92 (1.56–2.59)	2.38 (1.63–4.07)	2.89 (1.87–4.60)
Nails (μmol/kg)	19.7 ± 7.3	14.4 ± 2.3	17.5 ± 3.4	24.7 ± 7.6
	17.5 (10.6–48.4)	14.2 (10.6–19.6)	16.9 (13.4–27.0)	23.4 (15.0–48.4)
Urine (μmol/d)	2.14 ± 1.45	1.11 ± 0.46	2.38 ± 1.40	2.76 ± 1.56
	1.61 (0.31–7.02)	1.11 (0.31–2.52)	1.97 (0.84–5.94)	2.67 (0.31–7.02)
Intake (μmol/d)‡	3.04 ± 1.81	1.73 ± 0.62	3.15 ± 1.39	4.17 ± 1.95
	2.49 (0.86–9.20)	1.47 (0.86–3.36)	3.17 (1.20–5.64)	4.12 (1.08–9.20)

* $\bar{x}$ ± SD; median (and range) are below $\bar{x}$ ± SD.
† n = 63.
‡ One subject per household saved duplicate food plates. Number of subjects in each category was 76, 29, 15, and 32, respectively.

from up to eight 1-d food collections for year-1 subjects and up to four 1-d collections for year-2 subjects. Average intakes were based on ≥ 6 d of collection for year-1 subjects; in year 2 only two subjects' intakes were based on < 3 d of collection (2 d each). The average values of intake and concentrations in blood, urine, and toenails were considered in all subsequent analyses.

The results of the clinical laboratory tests were examined in relation to indicators of selenium intake, age, sex, and smoking status in ordinary least-squares multiple regression models (14) using *SAS* software (15). Each model evaluated included one indicator of selenium intake: either dietary selenium or the selenium concentration in serum, whole blood, or toenails. Age was included in the models as a continuous variable, and sex and smoking status (current smoker or not) were represented by indicator variables. Logarithmic transformations of selected clinical laboratory results were performed to normalize their distributions before they were included in the regression analysis, as noted in the tables. The regression coefficients calculated from the models are the predicted change in the laboratory value associated with a one-unit increment in the selenium measure. If the 95% confidence interval around the coefficient excludes 0, the association is statistically significant at the P = 0.05 level.

The average frequency of each symptom included in the questionnaire was calculated for each subject. For year-1 subjects the average was calculated on the basis of responses to four questionnaires; for year-2 subjects the average was calculated from the responses to two questionnaires. The occurrence of symptoms more frequent than the median was treated as a binomial dependent variable and examined in relation to indicators of selenium intake, age, sex, and smoking in logistic regression models (16) by using *GLIM* software (17). Age, sex, and smoking status were represented as in the linear-regression models. The presence or absence of abnormalities on physical examination, including those recorded by the dermatologist, were also treated as binomial independent variables and analyzed in relation to indicators of selenium intake, age, sex, and smoking in logistic-regression models. The results of the analyses for both symptoms and physical findings were presented as the relative odds of having frequent symptoms or abnormal physical findings associated with an increase in selenium amount of ~1 SD. Thus, we have presented the relative odds of having frequent symptoms or abnormal physical findings associated with an increase in whole-blood selenium of 1.27 μmol/kg, in serum selenium of 0.63 μmol/L, in nail selenium of 6.36 μmol/kg, or in dietary selenium of 1.27 μmol/d (100 μg/d).

Examining the increase in frequency of symptoms or abnormal physical findings in relation to a fairly large increase in indicator of selenium intake (1 SD) puts the odds ratios on a scale that is more intuitively meaningful than if results were expressed in untransformed units of intake. For example, an odds ratio > 1 indicates that a substantial increase in amount of selenium was associated with an increase in the frequency of symptoms. The further the odds ratio is from 1, the greater the strength of the association. If the 95% confidence interval around the odds ratio excludes 1, the association is statistically significant at the P = 0.05 level.

Results

In the first year we enrolled 78 subjects, of whom 49 were selected at random and 29 were from ranches where selenium toxicity in livestock had occurred. In the second year 64 ranchers were enrolled who had a serum selenium concentration at screening > 2.10 μmol/L. The mean age of the 142 subjects was 50 y (range 22–82 y), 47% of subjects were male, and 21% were current smokers. The average height of subjects was 1.67 m and the average weight was 74 kg. All subjects were white. Eighty-eight percent of all subjects asked to participate did so. Ninety-seven percent of subjects lived at their current address for ≥ 2 y. None of the subjects took selenium supplements. Ninety-seven percent of the ranchers ate beef from their ranch.

The average selenium concentrations of whole blood, serum, toenails, 24-h selenium excretion in urine, and daily dietary selenium intake are presented in **Table 2.** The mean selenium values were lowest for subjects selected at random and highest for ranchers who were enrolled in the study because of high serum selenium values found by screening. Among the subjects who collected food samples, selenium intake was > 2.54 μmol/d (200 μg/d) in about half. Twelve of the 76 subjects (16%) whose selenium intake was measured had average intakes > 5.09 μmol/d (400 μg/d).

TABLE 3
Pearson correlation coefficients between selenium concentrations in whole blood, serum, toenails, urine, and diet*

	Whole blood (μmol/kg)	Serum	Toenails	Urine
Serum (μmol/L)†	0.97			
Toenails (μmol/kg)†	0.91	0.89		
Urine (μmol/d)†‡	0.66	0.62	0.60	
Diet (μmol/d)§	0.69	0.63	0.69	0.86
Diet ($\mu mol \cdot kg^{-1} \cdot d^{-1}$)§	0.76	0.73	0.72	0.79

* All $P < 0.001$. Based on mean values of all specimens collected from each subject.

† $n = 141$.

‡ The correlations of urine selenium expressed as $\mu mol \cdot kg^{-1} \cdot d^{-1}$ with other indices were virtually the same as those shown. $n = 142$ for toenails.

§ $n = 76$.

The concentration of selenium in whole blood, serum, urine, and nails and the amount in the diet were all highly correlated (**Table 3**). The urine specimens and half of the duplicate food plates were collected over the same 1-d period, and this may account for the high correlation between selenium intake and urine selenium concentration. Selenium intake expressed per kilogram body weight was more highly correlated with blood selenium concentrations than was absolute intake. [The correlations in Table 3 are similar to those reported by Yang et al (18), although among the Chinese the higher correlations between diet and whole-blood selenium (0.96) and between urine and serum selenium (0.97) were probably due to the greater range in selenium intake in that population.] The relationship of selenium concentrations in blood and nails to dietary intake, age, sex, and smoking among a subset of subjects in the current study was examined in detail elsewhere (19).

In the presentation of laboratory results, signs, and symptoms in relation to selenium indices (**Tables 4–6**), we included as selenium indices whole blood, nails, and intake. Because whole-blood and serum selenium concentrations were particularly

TABLE 4
Regression coefficients (×1000) (and 95% confidence limits) for the association between laboratory test results and selenium concentrations in whole blood, nails, and diet*

Outcome variable (result)†	Predictor variable		
	Whole blood (μmol/kg)	Nails (μmol/kg)	Diet (μmol/d)
Tests reflecting liver function			
Prothrombin time (11.7 ± 0.9 s)‡	57.4	10.2	1.18
	(−65.3, 181.0)	(−16.5, 37.2)	(−165.0, 173.0)
Alanine aminotransferase (0.17 ± 0.11 μkat/L)	6.45	0.590	19.7§
	(−7.55, 21.2)	(−2.12, 3.30)	(8.65, 29.9)
Aspartate aminotransferase (−1.1 ± 0.3 μkat/L)∥	27.5	5.66	50.3§
	(−4.72, 59.8)	(−0.511, 11.8)	(14.9, 86.5)
Gamma glutamyltransferase (0.22 ± 0.19 μkat/L)	6.45	0.197	2.36
	(−17.3, 29.9)	(−4.17, 4.17)	(−27.5, 31.5)
Alkaline phosphatase (0.079 ± 0.28 μkat/L)∥	0.653	0.614	−28.3
	(−31.5, 33.0)	(−5.58, 6.76)	(−59.0, 2.36)
Tests reflecting hematologic function			
Leukocyte count (1.8 ± 0.3 10^9/L)∥	24.4	2.60	−10.2
	(−4.72, 54.3)	(−3.15, 8.65)	(−42.5, 22.0)
Hemoglobin (150.0 ± 16.0 g/L)	55.8	−102.0	−771.0
	(−1570.0, 1650.0)	(−417.0, 205.0)	(−2520.0, 1020.0)
Hematocrit (0.43 ± 0.04)	−2.83	−0.865§	−5.35
	(−7.39, 1.73)	(−1.73, −0.0173)	(−11.0, 0.126)
Tests performed as a general screen¶			
Sodium (140.0 ± 3.0 mmol/L)	−236.0	−62.1§	−181.0
	(−558.0, 77.1)	(−126.0, −1.34)	(−472.0, 118.0)
Potassium (4.5 ± 0.5 mmol/L)	102.0§	13.4§	39.3
	(48.0, 165.0)	(2.05, 25.1)	(−23.6, 102.0)
Chloride (106.0 ± 4.0 mmol/L)	−393.0	−94.4§	−189.0
	(−865.0, 40.9)	(−181.0, −13.4)	(−629.0, 252.0)

* Adjusted for age, sex, and smoking in a least-squares model. For the regressions with whole blood and nails, $n = 121$–139, with most including 139; for regressions with diet, $n = 68$–76, with most including 76.

† $\bar{x} \pm$ SD. Examined but not associated with selenium concentration: total protein, albumin, albumin-globulin ratio, lactic dehydrogenase, bilirubin, mean corpuscular volume, calcium, phosphorus, uric acid, glucose, blood urea nitrogen, cholesterol, creatinine, triglycerides, and creatinine phosphokinase.

‡ Adjusted for control prothrombin time.

§ $P < 0.05$ (confidence limits that exclude 0 indicate statistical significance at the 0.05 level).

∥ Coefficients and means refer to natural logarithm of outcome variable.

¶ Only results with regression coefficients that were statistically significant for at least one predictor variable are shown. A complete list of tests is given in the Appendix.

TABLE 5

Odds ratio (and 95% confidence interval) of having symptoms more frequently than the median for an increase of ~1 SD in concentration of selenium in whole blood, toenails, or diet*

Outcome variable (symptom)†	Predictor variable: Whole blood (n = 141)	Nails (n = 142)	Diet (n = 76)
Muscle twitches	1.17 (0.84–1.64)	1.10 (0.80–1.51)	1.28 (0.87–1.88)
Needed help getting out of chair	0.77 (0.41–1.44)	0.64 (0.31–1.31)	0.54 (0.20–1.42)
Paresthesias	0.64‡ (0.45–0.93)	0.53‡ (0.36–0.80)	0.72 (0.50–1.05)
Lethargy	1.41‡ (1.01–1.96)	1.41‡ (1.02–1.95)	1.43 (0.98–2.09)
Abdominal cramps	1.02 (0.74–1.40)	0.86 (0.62–1.19)	1.35 (0.94–1.95)
Nail breakage	0.72 (0.50–1.02)	0.79 (0.56–1.10)	0.84 (0.57–1.23)
Nail loss	1.22 (0.56–2.66)	1.13 (0.52–2.42)	0.78 (0.09–6.59)
Dark nail lines	0.77 (0.39–1.53)	0.75 (0.39–1.44)	0.85 (0.42–1.72)
White nail lines	1.09 (0.74–1.60)	1.01 (0.68–1.49)	1.20 (0.80–1.78)
Hair loss	1.13 (0.77–1.67)	1.04 (0.70–1.54)	0.96 (0.61–1.53)
Yellowed skin	0.38 (0.06–2.46)	0.50 (0.09–2.91)	0.86 (0.08–8.81)
Took medicine for rash	0.76 (0.49–1.18)	0.50 (0.28–0.88)	0.75 (0.45–1.25)
Garlic breath	1.14 (0.76–1.73)	1.03 (0.68–1.56)	1.03 (0.65–1.63)
Dizziness	1.20 (0.88–1.64)	1.29 (0.94–1.76)	1.17 (0.82–1.66)

* Odds ratio adjusted for age, sex, and smoking in a logistic regression model. Approximate 1 SD increments were whole blood, 1.27 μmol/kg; nails, 6.36 μmol/kg; and diet, 1.27-μmol/d.

† Results for symptoms where the a priori evidence supporting an association with selenium intake was weak and the odds ratios were 0.8–1.2 with 95% confidence intervals that included 1 are not shown. These were difficulty concentrating, need to take antacids, vomiting, hair dryness, metal taste in mouth, muscle cramps, depression, apathy, heartburn, diarrhea, and arthritis.

‡ $P < 0.05$.

highly correlated and because the relation of serum and whole-blood selenium to laboratory results, signs, and symptoms were essentially identical, we omitted presenting results pertaining to serum selenium. Further, we did not investigate the relation of urine selenium values to laboratory results, signs, and symptoms because the other indices probably reflected chronic selenium intake more accurately.

Several statistically significant associations were observed between selenium indices and laboratory results, but each was explained as due to other factors or to a single influential observation or was of such small magnitude as to be biologically inconsequential, as described below. Serum aminotransferase concentration was associated with selenium intake (Table 4). Because aminotransferases can be elevated by muscle trauma, which in turn may be related to ranching activities, we repeated the analyses including an indicator variable (rancher or non-rancher) to control for whether the subjects were randomly selected. This did not reduce the statistical significance of the association with alanine aminotransferase (ALT), although after this adjustment aspartate aminotransferase (AST) concentration was no longer significantly associated with selenium intake (P = 0.18). Likewise, when we controlled for alcohol intake in the analysis, the association of ALT with selenium intake was still present. Further, the association was not due to the effect of any single influential observation. The association observed was among subjects with ALTs in the normal range. Two subjects had ALTs above the normal range (0.02–0.50 μkat/L), but selenium intake was not measured in either subject. No subject had a markedly elevated aminotransferase concentration.

The association between nail selenium and hematocrit was no longer statistically significant after one single influential observation was excluded from the analysis. The previously reported association between leukocyte count and selenium indices, found in a preliminary analysis based on data from year-1 subjects only (20), was not present when the entire group of subjects was included in the analysis.

The relation of serum potassium to whole-blood and nail selenium almost certainly was due to hemolysis. The homes of the subjects selected at random were closer to the laboratory (average distance 39 km) than were the homes of the ranchers (average distance 209 km); transit time to the laboratory and the opportunity for hemolysis was greater for the blood specimens from ranchers. In the analysis of serum potassium concentration in relation to selenium indices, including the distance of the subject's home from the laboratory as a variable in the model removed the potassium-selenium association.

The associations between selenium indices and sodium and chloride were no longer statistically significant when one single influential observation was excluded from the analysis. The importance of the associations of sodium and chloride was further diminished in light of the absence of an a priori hypothesis that these values would be related to selenium indices.

In Table 5 the results relating the frequency of symptoms to selenium indices are presented. With the exceptions of paresthesias and lethargy, symptoms were not related to selenium indicators. The frequency of paresthesias was significantly less with increasing concentration of selenium in whole blood and nails, an association opposite to that expected for toxicity. This association was not due to the effect of any single influential observation. However, when we controlled for rancher-non-

TABLE 6

Odds ratio (and 95% confidence interval) of having abnormal findings on photographic examination of thumbnails associated with an increase of ~1 SD in concentration of selenium in toenails*

Leukonychia	0.95 (0.53–1.72)
Transverse ridging	0.55 (0.25–1.25)
Longitudinal ridging	0.57 (0.19–1.65)
Onycholysis	1.16 (0.48–2.79)

* Adjusted for age, sex, and smoking in a logistic regression model. Approximate 1 SD increment for toenail selenium was 6.36 μmol/kg. n = 142.

rancher status in the analysis, paresthesias were no longer strongly related to any of the selenium indices ($P > 0.07$). The odds of feeling lethargic more frequently than the median increased with increasing concentration of selenium in the whole blood and nails. When one influential observation was excluded from the analysis, the statistical significance of the association of lethargy with selenium indices was somewhat reduced (eg, for whole-blood selenium, $P = 0.06$). With the influential observation included and the addition of an indicator variable for rancher-nonrancher status, lethargy was no longer strongly related to any of the selenium indices ($P > 0.13$).

Most findings on physical examination had sufficient variation to support a statistical analysis (*see* Appendix). These findings showed no statistically significant association with concentration of selenium in whole blood, nails, or diet. In particular, nail abnormalities on photographic examination were not related to selenium concentration (Table 6).

Several findings on physical examination were too infrequent to support a meaningful statistical examination of their variation in relation to selenium indices. Nail loss, alopecia, liver enlargement, and muscle fasciculation were not noted in any of the subjects. Yellowed sclera were noted in two subjects, abnormal proprioception in two subjects, and abnormal muscle strength to extend the fingers in three subjects. However, the whole-blood selenium concentrations of all these subjects were < 3.18 μmol/kg. One subject had easy epilation and a whole-blood selenium concentration of 3.88 μmol/kg.

Discussion

The average daily selenium intake in this population was ~3.03 μmol/d (239 μg/d), much higher than the national average, which has been estimated to be 0.76–2.03 μmol/d (60–160 μg/d) (21–23). The average whole-blood selenium concentration in the study population (4.04 μmol/kg) was 54% greater than the average concentration of subjects in 19 US cities (2.61 μmol/L) (24). Thus, we were successful in identifying a population that had an unusually high selenium intake.

In this population we found no compelling evidence that the relatively high intake of selenium had had any adverse effects. The associations observed between abnormalities and selenium concentrations in most cases appeared to be either due to differences other than selenium intake between ranchers and randomly selected subjects or due to the effect of a single influential observation in a given analysis. None of the associations were noted for all indices of intake. Further, because a large number of associations were examined, by chance alone one might expect some to be statistically significant.

We hypothesized a priori that high selenium intake would adversely affect the liver. We observed an association of selenium intake with ALT. The regression equation predicted an increase of in ALT of 0.25 nkat/L associated with an increase in selenium intake of 0.0127 μmol/d (1 μg/d). Thus individuals at the extremes of the intake distribution from this study (0.86–9.20 μmol/d, or 68–724 μg/d) would be predicted to have a 0.16 μkat/L difference in ALT, a clinically insignificant change. The prolonged prothrombin times observed by Yang et al (8) in subjects with selenium intake > 10.8 μmol/d (850 μg/d) were not present in these data.

The relation of selenium intake to toxicity was evaluated in other studies. In previous studies in South Dakota, signs and symptoms of selenium toxicity were examined in relation to urine selenium concentration (5, 6); urine concentrations of 2.54–25.2 μmol/L were observed as were pathologic nails and other symptoms suggestive of selenium toxicity. (In the present study the range of urine selenium concentration was 0.13–5.85 μmol/L.) However, in the previous studies no relation between the urine selenium concentrations and signs and symptoms was established. Because urine selenium concentration was the only index of selenium intake available in those studies, strong assumptions about urine output and constancy of selenium excretion would be needed to use the data to address the issue of maximal safe intake.

Yang et al (8), in an investigation similar to ours, found that selenium intake > 10.8 μmol/d (850 μg/d) was associated with an increased prothrombin time and that the nail abnormalities characteristic of selenosis appeared at intakes > 11.5 μmol/d (910 μg/d). Yang et al (8) also found that several biochemical indices reflecting selenium metabolism were altered at intakes > 9.53 μmol/d (750 μg/d). An association between ALT and selenium intake was not observed. Among the ~30 subjects in that study with selenium intakes between 2.54 and 6.36 μmol/d (200 and 500 μg/d), no evidence of selenium toxicity was found; few subjects had intakes between 6.36 and 9.53 μmol/d (500 and 750 μg/d).

Other reports corroborate Yang et al's findings (8) that clinical selenosis occurs at intakes > 10.8 μmol/d (850 μg/d). A Chinese man consuming 11.4 μmol/d (900 μg/d) of inorganic selenium for 2 y developed pathologic nail changes (7). Selenium supplements that contained up to 343 μmol/tablet (27 mg/tablet), because of a manufacturing error, resulted in nausea, abdominal pain, diarrhea, hair and nail changes, peripheral neuropathy, fatigue, and irritability in 13 subjects, each of whom ingested up to 77 tablets (9). For an extensive review of selenium toxicity in humans and animals, the reader is referred to Olson (25).

In a recent study of 134 Venezuelans (children and adults), selenium intake was estimated to be 3.81–5.09 μmol/d (300–400 μg/d) (26). Although nausea, pathologic nails, and loss of hair occurred in several subjects, selenium intake and concentration in blood were not examined in relation to these signs and symptoms. A previous study of children from the same seleniferous area suggested that a moderately elevated selenium intake (probably < 10.8 μmol/d, or 850 μg/d) resulted in toxicity (27). However, the authors noted that factors other than selenium intake may have been responsible for the signs and symptoms observed.

Sakura and Tsuchiya (28) suggested that an upper limit of selenium intake of 6.36 μmol/d (500 μg/d) be adopted on the basis of estimates that some Japanese fishermen chronically consume that amount. Although no selenium toxicity was reported for the fishermen, they were not surveyed for signs or symptoms, and the bioavailability of selenium from some fish and seafoods may be low (29, 30).

In a recent study from Denmark, a decrease in serum somatomedin C was observed in subjects who consumed 3.25 μmol/d (256 μg/d) of organic selenium for 6 mo (31). In the present study population, however, evidence of a relationship between plasma somatomedin C concentration and selenium indices was not present (32). Although there may be subclinical manifestations of moderately high selenium intake that would have gone undetected in the current study, we found no evidence of toxicity from selenium in subjects whose intake was as high as 9.20 μmol/d (724 μg/d).

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APPENDIX

Clinical laboratory tests, symptoms, and physical examination findings that were examined in relation to amounts of selenium in the blood, nails, and diet

Laboratory tests	Prothrombin time, total protein, albumin, albumin-globulin ratio, lactic dehydrogenase, bilirubin, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, leukocyte count, hemoglobin, hematocrit, mean corpuscular volume, calcium, phosphorus, uric acid, sodium, potassium, chloride, glucose, blood urea nitrogen, creatinine phosphokinase, cholesterol, creatinine, triglycerides
Symptoms	Muscle cramps, muscle twitches, need help getting out of chair, paresthesias, lethargy, depression, apathy, difficulty concentrating, abdominal cramps, heartburn, need to take antacids, vomiting, diarrhea, nail breakage, nail loss, dark nail lines, white nail lines, hair dryness, hair loss, yellowed skin, took medicine for rash, metal taste in mouth, garlic breath, dizziness, arthritis
Physical findings*	Biceps reflex, triceps reflex, supinator reflex, knee jerk, ankle jerk, ankle flex, extensor hallicus longus, distal light touch, distal pin prick, vibratory sense, stereognosis, missing or carious teeth, complete dentures, thickened nails, horizontal nail lines, transverse nail lines, cataracts, garlic breath odor, dermatitis, folliculitis, photographic exam: leukonychia, transverse ridging, longitudinal ridging, onycholysis

* Findings that were too infrequently abnormal to support a meaningful statistical examination in relation to selenium indices were nail loss, alopecia, hepatomegaly, muscle fasciculation, yellowed sclera, abnormal proprioception, abnormal strength of the muscles that extend the fingers, and easy epilation.